PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	22 FEB 2006
Applicant's or agent's file reference BIOL0004WO	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/10946	15 April 2004 (15.04.2004)	16 April 2003 (16.04.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): C07H 21/04 and US Cl.: 536/24.5

Applicant

ISIS PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	27 January 2006 (27.01.2006)	Jon B. Ashen Telephone No. 703-308-1235

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/10946

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-18 and 23

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/10916

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-18 and 23	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-18 and 23	NO
Industrial applicability (IA)	Claims 1-18 and 23	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-18 and 23 lack novelty under PCT Article 33(2) as being anticipated by Miraglia et al. (US 6,184,212). The instant claims are drawn to a compound 8-80 nucleotides in length targeted to a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO: 4) (claim 1). Subsequent dependent claims require that the claimed comounds are of a particular length, are RNA or DNA, are chimeric of a specfied structure, have 70-95% complementarity with instant SEQ ID NO: 4, comprise specified modifications to the sugar, nucleobase or internucleoside linkages and is comprised in a kit (2-18 and 23). Miraglia et al. disclose SEQ ID NO: 250, a chimeric gapmer antisense oligonucleotide that has 20 nucleobases and is 100% complementary to instant SEQ ID NO: 4 and that the antisense oligonucleotides of their invention can be comprised in a kit (Cols. 39-40, SEQ ID NO: 250 in Table 11 and col. 5, lines 45-60). The antisense oligonucleotide disclosed by Miraglia et al. meets all the structural limitations of the instant claims and is therefore, absent evidence to the contrary, an antisense oligonucleotide targeted to a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO: 4) (claim 1).

Claims 1-18 and 23 lack novelty under PCT Article 33(2) as being anticipated by Monia et al. (US 6,300,132). The instant invention as set forth in claims 1-18 and 23 is set forth above. Monia et al. disclose SEQ ID NO: 73, a chimeric gapmer antisense oligonucleotide that has 20 nucleobases and is 100% complementary to instant SEQ ID NO: 4 and that the antisense oligonucleotides of their invention can be comprised in a kit (Col. 40, Example 15; col. 41, Table 1, SEQ ID NO: 73; and col. 12, lines 30-45). The antisense oligonucleotide disclosed by Miraglia et al. meets all the structural limitations of the instant claims and is therefore, absent evidence to the contrary, an antisense oligonucleotide targeted to a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO: 4) (claim 1).

Claims 1-18 and 23 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.